Page 1 of 21 APPLICATION NOL ATTY, DOCKET NO. 2 9 1998 0609.4270001 FORM PTO-1449 APPLICANT GROUP\_1800 TANZI and KIM INFORMATION DISCLOSURE STATEMENT GROUP 1648 / 6444 FILING DATE April 24, 1998 U.S. PATENT DOCUMENTS DOCUMENT NUMBER DATE NAME CLASS SUB-CLASS FILING DATE FOREIGN PATENT DOCUMENTS DOCUMENT NUMBER DATE COUNTRY CLASS SUB-CLASS TRANSLATION Yes No Yes No Yes No Yes No Yes No OTHER (Including Author, Title, Date, Pertinent Pages, etc.) Borchelt, D.R., et al., "Familial Alzheimer's Disease-Linked Presenilin 1 Variants Elevate Aß1-42/1-40 Ratio In Vitro and In Vivo," Neuron 17:1005-1013 (November 1996) Bush, A.I., et al., "An Abnormality of Plasma Amyloid Protein Precursor in Alzheimer's Disease," Annals of Neurology 32:57-65 (1992)

Chinnaiyan, A.M., and Dixit, V.M., "The cell-death machine," Current Biology 6:555-562 (May 1996)

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xc	АТ	2	Cook, D.G., Localizatio	pok, D.G., et al., "Expression and analysis of presentlin 1 in a human neuronal system: ocalization in cell bodies and dendrites," <i>Proc. Natl. Acad. Sci. USA 93</i> :9223-9228 (August 1996)						
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KC	AS	8 Kim, TW Associate	., et al., "Proteol d Presenilin 1 and	ytic Processing and Ubiqui 2," Soc. Neurosci. Abstr. 2	tin-Depender 22:7 <b>2</b> 7, Abst	nt Degradation of ract No. 293.5 (N	Alzheimer- ovember 1996)			
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KC	AS	<u>18</u>	Phosphoryla	Walter, J., et al., "The Alzheimer's Disease-Associated Presenilins Are Differentially Phosphorylated Proteins Located Predominantly within the Endoplasmic Reticulum," Molecular Medicine 2:673-691 (November 1996)										
KC		<u>18</u>	Proteolysis	Wang, X., et al., "SREBP-1, a Membrane-Bound Transcription Factor Released by Sterol-Regulated Proteolysis," <i>Cell</i> 77:53-62 (1994)										
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